

Could Malaria Reappear in Italy?

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Because of concern about the possible reintroduction of malaria transmission in Italy, we analyzed the epidemiologic factors involved and determined the country's malariogenic potential. Some rural areas in central and southern Italy have high receptivity because of the presence of potential malaria vectors. *Anopheles labranchiae* is probably susceptible to infection with *Plasmodium vivax* strains, but less likely to be susceptible to infection with *P. falciparum*. Its vulnerability is low because of the low presence of gametocyte carriers (imported cases) during the season climatically favorable to transmission. The overall malariogenic potential of Italy appears to be low, and reintroduction of malaria is unlikely in most of the country. However, our investigations showed that the malaria situation merits ongoing epidemiologic surveillance.

At the end of World War II, malaria was still present in vast areas of Italy, mainly in the central and southern regions and major islands and along northeastern coastal areas, with offshoots of hypoendemicity in the Pianura Padana (1). The three vectors were *Anopheles labranchiae* Falleroni and *An. sacharovi* Favre, both belonging to the so-called *maculipennis* complex, and *An. superpictus* Grassi (2). *An. labranchiae* was the principal vector in the central and southern coastal areas, Sicily, and Sardinia. In the two islands, the species was found as high as 1,000 meters above sea level. *An. sacharovi* was present along much of the coastal area and in Sardinia, but was most important as vector in the plains of the northeastern Adriatic coast, where *An. labranchiae* was absent. *An. superpictus* was considered a secondary vector in central and southern Italy and Sicily. In some interior areas of the Pianura Padana, where none of the three vectors was present, low levels of endemicity were probably maintained by other species belonging to the *maculipennis* complex.

A malaria eradication campaign launched in 1947 led to interruption of transmission of *Plasmodium falciparum* malaria throughout Italy within 1 year (3). Indoor treatment with DDT (2 g of active ingredient per m²) of houses, stables, shelters, and all other rural structures continued into the mid-1950s and even later in some hyperendemic areas. In Sardinia, where transmission was particularly high, a special program was carried out to eradicate the vector (4). The last endemic focus of *P. vivax* was reported in the province of Palermo, Sicily, in 1956 (5), followed by sporadic cases in the same province in 1962 (6). The World Health Organization declared Italy free from malaria on November 17, 1970. Since then, almost all reported cases have been imported, but their number has risen steadily over the last decade (7,8).

In 1997, a case of introduced malaria occurred in a rural area of Grosseto Province, the first since the eradication of malaria from Italy (9). This event, along with the occasional presence of *Plasmodium* carriers who contracted the disease in malaria-endemic areas and the increasing number of immigrants from malaria-endemic countries entering Italy, raises concern about the possible reappearance of malaria foci in certain areas. We evaluate the malariogenic potential of Italy and assess the risk for malaria transmission in some areas, decades after the last analysis of the problem (10,11).

Material and Methods

The risk of malaria being reintroduced to an area can be calculated by determining its "malariogenic potential," which is influenced by three factors: receptivity, infectivity, and vulnerability. Receptivity takes into account the presence, density, and biologic characteristics of the vectors; infectivity is the degree of susceptibility of mosquitoes to different *Plasmodium* species; and vulnerability is the number of gametocyte carriers present in the area.

Receptivity

To evaluate Italy's receptivity, we analyzed historical data and the results of entomologic surveys carried out in Italy as part of epidemiologic investigations over the last 20 years. The vectorial capacity of some Italian populations of *An. labranchiae* was also estimated by the MacDonald formula (12).

Infectivity

The possibility that the sporogonic cycle of the various *Plasmodium* species may be completed within a vector is defined as infectivity. Only a few species of the *Anopheles* genus are capable of becoming infected and transmitting malaria. Furthermore, for genetic reasons, even mosquito populations of the same species can differ in sensitivity to plasmodia (13) or may be completely resistant to infection with plasmodia from the same species but different

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geographic areas. Infectivity in a mosquito population is a determining factor in the assessment of malariogenic potential in a given area. We analyzed data in published studies to evaluate the infectivity of Italian vectors.

Vulnerability

Vulnerability in a given territory is determined by the number of gametocyte carriers during the period in which malaria transmission is possible. To determine the degree of Italy's vulnerability, a sample of malaria cases reported from 1989 to 1996 was selected on the basis of spatial and temporal risk factors for the transmission of malaria. Malaria cases reported in Italy in 1997 were also analyzed. Because of the limited distribution of vectors potentially capable of transmitting malaria, we considered only cases in Tuscany, Campania, Abruzzo, Molise, Basilicata, Apulia, Calabria, Sicily, and Sardinia. In the past, the season of malaria transmission in central and southern Italy lasted from June to late September for *P. vivax* and from July to early September for *P. falciparum*. We therefore selected cases reported from June through September.

Results

Receptivity

After their drastic reduction as a result of the DDT campaign, the endophylic anopheline species have begun to reproduce again and in many cases have reached preintervention densities (14). Of the anopheline species that had been vectors of malaria in Italy, only *An. labranchiae* and *An. superpictus* are still present in epidemiologically relevant densities (14). In other European and Mediterranean countries, other anophelines have been considered sec-

ondary (*An. atroparvus* and *An. melanoon*) and occasional (*An. algeriensis*, *An. hyrcanus*, and *An. claviger*) malaria vectors. *An. sergenti*, a north African species, was implicated in the 1960s in the transmission of a few sporadic case of malaria on the island of Pantelleria (15).

Distribution and Density of Potential Vectors

In northern Italy, in particular the northwestern regions (Veneto and Emilia) where *An. sacharovi* was present, the last specimens of the vector were found in the province of Rovigo (16); in the last 30 years there have been no further records. No *An. sacharovi* larvae or adults were recorded in a recent survey along the northwestern coast of Italy (17). However, areas with epidemiologically relevant anopheline densities still exist in Tuscany (only in Grosseto Province), Calabria, Puglia, Sicily, and Sardinia (14), where hydrogeologic or environmental characteristics are conducive to the development of vectors (Table 1). Residual populations of *An. labranchiae* and *An. superpictus* could still be present along the coasts of Abruzzo, Molise (east coast), Campania, and Basilicata (west coast), but no relevant densities have recently been reported.

Vectorial Capacity (VC)

The high density of anopheline populations reported in some areas of Italy does not necessarily imply the resumption of malaria. Other entomologic factors must be taken into consideration to estimate the risk of transmission. The VC of a mosquito population is the measure used in epidemiology to estimate risk in various geographic areas. It expresses the number of potentially infective bites that originate daily from a case of malaria in a given area or, more precisely, from a carrier of gametocytes capable of infecting all the

Table 1. Distribution and density of *Anopheles labranchiae* and *An. superpictus* in five regions of central, southern, and insular Italy

Region	At-risk areas	Vector	Larval breeding sites ^a	Vector density and capacity ^b
Tuscany	Grosseto province: areas of intensive rice cultivation (S. Carlo, Principina and S. Donato, Orbetello)	<i>An. labranchiae</i>	Rice fields, agricultural and land reclamation canals, wells. Larval densities in rice fields 5-10 larvae/sample, elsewhere 0.5-1 larvae/sample	100-1,000 per animal shelter; 180-200/person/night. VC in rice fields: <i>P. falc.</i> 7-26; <i>P. vivax</i> 8.3-32.5; VC in natural breeding sites: <i>P. falc.</i> 0.8-2.9; <i>P. vivax</i> 0.96-3.3
Apulia	Coastal plains of the Adriatic side, from Lesina Lake to Candelaro River	<i>An. labranchiae</i>	Land reclamation canals, pools for agricultural purposes. Larval densities 0.02-0.05 larvae/sample	20-30 per animal shelter
Calabria	Coastal plains of the Tirrenian and Ionian sides and the close hinterland	<i>An. labranchiae</i> <i>An. superpictus</i>	Larval densities: <i>An. labranchiae</i> 0.5-1 larvae/sample <i>An. superpictus</i> 0.06-0.1 larvae/sample	20-500 <i>An. labranchiae</i> , 2-10 <i>An. superpictus</i> per animal shelter. 10-20 <i>An. labr.</i> /person/night. VC of <i>An. labranchiae</i> for <i>P. falciparum</i> 0.8-8.9
Sicily	Rural coastal and hilly areas of the whole region	<i>An. labranchiae</i> <i>An. superpictus</i>	Rivers, streams, pools, and canals for agricultural purposes. Larval densities of <i>An. labranchiae</i> 0.03 to 0.5 larvae/sample	10-200 <i>An. labranchiae</i> per animal shelter
Sardinia	Rural coastal and hilly areas of the whole region	<i>An. labranchiae</i>	Mainly rivers and streams; ponds, artificial pools, rice fields and irrigation canals. Larval densities 1 to 10 larvae/sample	5-40 per animal shelter

^aFigures refer to areas considered as "at risk" for malaria reintroduction during surveys carried out from 1994 to 1996.

^bCalculated at a mean temperature of 25°C (July to August), assuming a sporogonic cycle of 11 days for *P. falciparum* and 10 days for *P. vivax*. VC = vectorial capacity.

receptive mosquitoes that feed on the carrier. VC is influenced by three factors: the anthropophily, longevity, and density of the vector. The few recent estimates of the VC of Italian anopheline populations have been limited to *An. labranchiae* (14,18). The first attempt was made in 1978 in Calabria: VC was reported as 0.82 to 8.9, with an average density of 16 bites per person per night (Coluzzi A. and M., unpub. data). In 1994, in a large area of rice cultivation in Tuscany (Grosseto Province), VC was very low in early July, constituting no real risk for malaria transmission (<0.01 for both *P. falciparum* and *P. vivax*). At the beginning and especially the end of August, VC was high (8 to 32.5), especially for *P. vivax*, which has a shorter sporogonic cycle than *P. falciparum* (VC 7 to 26). This high VC is undoubtedly influenced by the high number of bites per person per night (>200) reported in the area (14). In 1998 in the same province but in areas where only natural anopheline breeding sites are reported, we calculated the following VCs from mid-July through the end of August: *P. falciparum* 0.8 to 2.9 and *P. vivax* 0.96 to 3.3 (<10 bites/person/night) (18).

Infectivity

As *Plasmodium* species have long been eradicated in Italy, it is essential to determine whether local vectors are still sensitive to infection with *Plasmodium* from other areas where malaria is present. Few tests of infectivity have been carried out with potential Italian vectors. There are numerous difficulties in rearing mosquitoes of the *An. maculipennis* complex, obtaining blood with vital gametocytes, and setting up an efficient artificial system that anophelines bite. To resolve these technical difficulties, some samples of *An. atroparvus* and *An. labranchiae* were captured in Italy in the 1970s and transported on several occasions to Kenya, where they were induced to bite *P. falciparum* carriers (19,20). In none of the mosquitoes did the plasmodia carry out the entire cycle and reach the salivary glands. These susceptibility tests were, of course, carried out with an extremely low number of samples and are insufficient to confirm that Italian anopheline populations are entirely resistant to infection with African strains of *P. falciparum*. Nevertheless, data on the resistance of Italian anopheline populations to tropical African *P. falciparum* strains agree with other observations made in England (21) and Portugal (20) on local *An. atroparvus* populations.

Populations of *An. atroparvus* from the eastern Russian Federation were sensitive to *P. vivax* strains from Southeast Asia (22), and populations from Romania were successfully infected with *P. vivax* strains from Korea (23). The marked tendency of Italian populations of *An. atroparvus* to bite animals, together with susceptibility assays carried out so far (19), does not indicate that this species is a malaria vector in Italy. As for *An. labranchiae*, this particularly anthropophilic Mediterranean species can certainly transmit *P. vivax*, as shown by the 1971 epidemic in Corsica (24), the cases reported in Greece during 1975–76 (25), and the recent sporadic case in Grosseto Province (9). The susceptibility of *An. superpictus* to *P. falciparum* of African origin has not been tested, but this mosquito is probably sensitive, as it belongs to the subgenus *Cellia*, to which the principal African malaria vectors also belong.

Vulnerability

Of 885 cases reported in 1997, only 88 (9.9% of the total) were reported from the nine regions at risk (Table 2). A total of 25 cases (2.8%) occurred during the season favorable to malaria transmission: 15 from *P. falciparum*, 9 from *P. vivax*, and 1 from *P. malariae*. Most of the patients (64%, $n=16$) lived in Tuscany. Considering that the highest anopheline mosquito densities were reported in this region, these results are cause for concern. On the other hand, the samples were quite small (16 patients) and other factors need to be considered. First is the number of patients who live in rural areas, since these are the only areas where the vector can come into contact with a gametocyte carrier. The analysis of samples shows that most of the 25 at-risk patients (72%, $n=18$) lived in an urban area. Another factor is the length of exposure of the malaria patients to mosquito bites during the disease or the length of their stay in a malaria-endemic area. In fact, all the patients received hospital care in urban areas, which would certainly limit mosquito-human contact. However, the factor that most affects a territory's vulnerability is the number of gametocyte carriers—the only persons who can infect mosquitoes—and the length of their potential exposure to mosquitoes. Of patients who lived in areas at risk and had contracted malaria during a period theoretically favorable to transmission, only eight became gametocyte carriers (six of them carriers of *P. vivax*). These carriers represent 0.7% of all malaria cases reported in Italy in 1997 and 4% of all the gametocyte carriers. In these patients, the average time between appearance of symptoms and malaria diagnosis (when therapy began) was 8.2 days, which is the period when patients could have been a source of infection for mosquitoes. The cases reported from 1989 to 1996 show similar results: of 5,012 cases, 522 (10.4%) occurred in central and southern Italy; only 184 of these occurred during high-risk months (June–September). Of 30 gametocyte carriers, 27 were of *P. vivax*, 2 of *P. falciparum*, and 1 of *P. ovale*.

Conclusion

We investigated Italy's malariogenic potential and the possibility of a recurrence of transmission there. Our results indicate the following conclusions. First, some rural areas in central and southern Italy have high receptivity because of the presence of potential malaria vectors with VC. The figures for VC were obtained by collecting mosquitoes on persons exposed to mosquito bites without any protection (14). These data are purely theoretical, as it would be quite

Table 2. Italy's vulnerability to malaria during the season favorable to malaria transmission (June to September) from 1989 to 1997

Year	Total no. of malaria cases	No. of cases in at-risk regions ^a	No. of cases in at-risk regions and favorable season	Total no. of gametocyte carriers	No. of gametocyte carriers in at-risk areas and season
1989–1996	5012	522	184	646	30
1997	885	88	25	148	8

^aNine regions in central, southern, and insular Italy.

unlikely for a person to remain exposed to mosquito bites for long without taking preventive steps. For comparison with the VC calculated in Italy with that of malaria-endemic areas, the VC of *P. falciparum* reaches values >10 and in some cases >30 in the hyperendemic conditions in many areas of the African savanna.

However, even a level of 0.1 (the average production of an infective bite from a malaria patient every 10 days) appears sufficient to maintain hyperendemicity, once the number of carriers of *P. falciparum* gametocytes reaches 50% of the population. The critical VC value (i.e., the level below which malaria does not remain endemic) has been calculated for the Garki region (Nigeria, State of Kano) as 0.022, or an average production of about 1 infective bite from a malaria patient every 50 days (26). In theory, therefore, the VC in some areas of Italy is epidemiologically significant, and these areas could become receptive.

Second, *An. labranchiae* is susceptible to infection with *P. vivax* strains from malaria-endemic areas, while infection with tropical African strains of *P. falciparum* seems less likely. Third, Italy's vulnerability is low because of the low presence of gametocyte carriers during the season climatically favorable to transmission in areas at risk. These figures are certainly underestimates, however, as in some regions of central and southern Italy not all malaria cases are reported, and the number of migrants from countries with endemic malaria, who come to Italy to work, is constantly increasing (7,8).

The overall malariogenic potential of Italy appears to be low, and malaria reintroduction is unlikely in most of the country. Sporadic autochthonous *P. vivax* malaria cases may occur but only in limited rural areas, where high densities of *An. labranchiae* have been reported. These results indicate the need for more epidemiologic surveillance, especially as the Italian situation is extremely dynamic and changeable. Sociopolitical factors, in particular, could lead to substantial changes in the flow of immigrants from endemic malaria areas, and environmental factors could result in changes in the density and distribution of vector populations.

Furthermore, the continuous contact of strains of exotic plasmodia with potential mosquito vectors could lead to long-term selection or adaptation of strains capable of developing in Italian mosquitoes. The possible presence in rural central and southern Italy of potential *P. vivax* carriers (e.g., immigrants from Asia and Africa hired as seasonal workers) is of concern.

A possible episode of autochthonous malaria transmission in Italy would not have serious health consequences, as it could easily and quickly be controlled by the National Health Service. The impact on Italy's image, however, could be serious at the international level. From an economic standpoint, reports of malaria cases would undoubtedly affect Italy's tourist industry.

To prevent and manage indigenous malaria cases in areas where the density of the vector is substantial, regional or local centers should be established with experts competent in epidemiologic surveillance and malaria control. These centers should also monitor the movements of malaria *Plasmodium* carriers in the country and assess the risk for malaria transmission in different regions.

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